



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07N 1/00, A61K 31/715		A1	(11) International Publication Number: WO 92/22585 (43) International Publication Date: 23 December 1992 (23.12.92)
(21) International Application Number: PCT/US92/04594			(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), NO, SE (European patent).
(22) International Filing Date: 5 June 1992 (05.06.92)			
(30) Priority data: 712,880 11 June 1991 (11.06.91) US 799,751 27 November 1991 (27.11.91) US			
(71) Applicant: PATENT BIOPHARMACEUTICS, INC. [US/US]; 2856 West 33rd Street, Erie, PA 16506 (US).			Published <i>With international search report.</i>
(72) Inventor: GALLINA, Damian, J. ; 2856 West 33rd Street, Erie, PA 16506 (US).			
(74) Agents: WHITE, Paul, E., Jr. et al.; Cushman, Darby & Cushman, Ninth Floor, 1100 New York Avenue, N.W., Washington, DC 20005-3918 (US).			

(54) Title: METHODS OF TREATING HEMORRHOIDS AND ANORECTAL DISEASE

(57) Abstract

A method of treating hemorrhoids and anorectal disease which includes applying to the hemorrhoids and anorectal tissues an effective amount of a composition including a pharmaceutically acceptable carrier and hyaluronic acid or pharmaceutically acceptable salts thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

METHODS OF TREATING HEMORRHOIDS AND
ANORECTAL DISEASE

BACKGROUND OF THE INVENTION

The present invention relates to methods
5 of treating hemorrhoids and diseases of the
anorectum employing novel pharmaceutical
compositions. In particular, the present invention
relates to topical applications of hyaluronate
preparations as rectal bonding and adhesion agents,
10 anti-inflammatory agents and bio-repair materials.
The use of hyaluronate preparations employs their
properties to reduce the inflammation, pain,
swelling, and sequelae of injured, irritated,
diseased, strained, or traumatized anorectal tissues
15 while adhering to and protecting sensitive tissues
of the anorectum. The source of the hyaluronate
used in the treatment compositions may be a
hyaluronic acid or any acceptable salt form of
hyaluronic acid. The term "hyaluronate" is often
20 used to mean "hyaluronic acid equivalent" which
equates to hyaluronic acid of varying molecular
weights and any of their salt forms.

Hyaluronic acid is a naturally occurring
25 mucopolysaccharide with a molecular weight generally
ranging between about 50,000 and 8,000,000 (or
possibly higher), depending on the sources of the
hyaluronate and the analytical methods used in its
determination.

Methods of obtaining highly-pure or ultra-
30 pure hyaluronic acid and its salt forms, isolation
techniques, and analytical methods for testing
purity are provided, for example, in the U.S.

patents, numbered 3,396,081, 4,141,973, 4,517,295, 4,736,024, 4,784,990 and 4,808,576.

Hyaluronic acid is well known, being found in the joint tissue and vitreous humor of the eyes of mammals. It has been extracted from rooster combs, human umbilical cords and bacterial cultures such as those of hemolytic group A and C streptococci for various therapeutic purposes. One of the first therapeutic uses of this material was as a replacement for the liquid vitreous of the human eye to aid in ophthalmic surgery, especially in the treatment of retinal detachment. It has also been used for the relief of trauma or irritation in joint tissue of mammals including humans by injection into the synovial fluid of the joint.

An extensive discussion of its various uses is found in U.S. Patent No. 4,141,973. The administration of hyaluronic acid alone and with cortisone in various animal joints, especially horses, is discussed in the article by Rydell et al., "Effect of Intra-articular Injection of Hyaluronic Acid on the Clinical Symptoms of Osteoarthritis and on Granulation Tissue Formation", Clinical Orthopaedics and Related Research, October, 25 1971, No. 80. The use of hyaluronic acid in human joints is reported in the "Preliminary Clinical Assessment of Na Hyaluronate Injection into Human Arthritic Joints" by Peyron et al., Pathologic Biologic, October, 1974, Vol. 22, No. 8. The use of hyaluronic acid in reducing fibrotic wound reactions is reported in the article by Rydell, "Decreased Granulation Tissue Reaction After Instillation of Hyaluronic Acid", Acta Orthop. Scandinav., Vol. 41.

Hyaluronic acid and derivatives thereof can play a critical role in wound healing. Hyaluronate preparations are already marketed by several companies as products utilized in eye 5 surgery, hip repair, dentistry, cosmetics, skin treatments, and dermatology.

U.S. Patent No. 4,736,024 describes the use of hyaluronic acid or a molecular weight fraction thereof as a vehicle for pharmacologically 10 active substances. The vehicle may be in suppository form for transcutaneous absorption to obtain a systemic effect. In contrast, the present methods of treatment employ the bonding, protective, healing, therapeutic, and curative properties of 15 hyaluronic acid and derivatives thereof for their direct, local therapeutic affect when applied topically to thrombosed anorectal vessels, inflamed tissues of the anorectum, rectal fissures, and/or pruritis ani. In the present invention, hyaluronic 20 acid (and its derivatives) is the active pharmaceutical agent.

For the present invention, pharmaceutical preparations containing less than 0.1% to more than 25.0% hyaluronate have been made and applied 25 topically to the anorectum in successfully relieving the tenderness, soreness, pain, burn, itch, and discomfort of inflamed, irritated anorectal tissues. Hyaluronate reduces pain, inflammation, and swelling due to its anti-inflammatory and membrane 30 stabilizing properties. Hyaluronate protects sensitive tissues and vessels of the anorectal epithelium and rectal mucosa by adhering to them and can remarkably mask the trauma of inflamed tissues.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating hemorrhoids and other anorectal diseases by topically applying to hemorrhoidal and anorectal tissues a pharmaceutical preparation comprising a 5 hyaluronate acid moiety such as hyaluronic acid or an acceptable salt form of hyaluronic acid, in an effective amount for the treatment of anorectal disease. The disease states of the anorectum include but are not limited to hemorrhoids, rectal 10 fissures, inflamed anorectal tissues, pruritis ani and proctitis.

It is accordingly one important object of the present invention to provide a method for 15 promoting the healing of traumatized, injured, irritated, inflamed, or diseased anorectal tissues while reducing the pain, burn, inflammation, itch, and swelling of these tissues by means of the topical application of a hyaluronate preparation. 20 The hyaluronate preparation displays a powerful anti-inflammatory action on anorectal tissues.

An important advantage of using 25 hyaluronate for anorectal treatment is that while sodium hyaluronate, for example, may be compared to hydrocortisone in its anti-inflammatory affect, unlike hydrocortisone or other glucocorticoids, sodium hyaluronate is not catabolic in nature. Hyaluronic acid and its derivatives stabilize 30 cellular membranes, reduce inflammation and enhance the anabolic process as opposed to the catabolic process.

It is a related object of the present invention to provide an improved method of treating hemorrhoids and other anorectal problems by utilizing the advantageous bonding and adhering properties as well as the anti-inflammatory and healing properties of hyaluronic acid and its various salt forms.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

10 Pain, discomfort, tenderness, inflammation, and swelling are reduced when hyaluronic acid or an acceptable salt form of hyaluronic acid are applied directly to irritated, inflamed, traumatized, strained, or injured tissues of the anorectum. One embodiment of the present invention is the use of hyaluronate in the treatment of hemorrhoidal and other anorectal disease conditions employing the anti-inflammatory property of hyaluronic acid and its derivatives.

20 Another embodiment of the present invention is to employ the property of hyaluronic acid and its derivatives to bond or strongly adhere to tissues of the anorectum in methods of treatment, which provides a protective coating on irritated, inflamed, sore, tender, and sensitive anorectal tissues, such as hemorrhoids.

25 A further embodiment of the present invention is to employ the property of hyaluronic acid and its derivatives to promote the healing of injured, irritated, strained, diseased or traumatized anorectal tissues.

Additional embodiments of the present invention include: (1) treatment of internal and external hemorrhoids; (2) treatment of inflamed anorectal tissues; (3) treatment of rectal fissures; 5 (4) treatment of pruritis ani; and (5) treatment of proctitis.

Any pharmaceutically acceptable form of hyaluronic acid may be used in the present invention. This application will for the most part, 10 however, be principally concerned with the representative use of the readily available commercial forms of hyaluronate, such as hyaluronic acid, the potassium salt of hyaluronic acid, and more preferably sodium hyaluronate. This in no way 15 limits the forms of hyaluronic acid employed in the present invention

Hyaluronic acid and derivatives thereof may be incorporated into numerous types of gels, 20 creams, ointments, lotions, pastes, salves, liquids, and/or solid suppository vehicles. Sterile distilled water alone and simple cream, ointment and suppository bases may be employed as carriers of the hyaluronic acid and derivatives. Examples of 25 suppository bases and suspending vehicles include Fattibase_{TM} (polyethylene glycol base), Vehicle-S_{TM} (acrylic polymer resin base), and Polybase_{TM} (polyethylene glycol base) by Paddock Laboratories, Inc., Minneapolis, Minnesota. Such pharmaceutically acceptable carriers are readily available for 30 preparing the present formulations and have desirable pH's, melting points, and preservatives.

In its more specific aspects, the preferred concentration of hyaluronate in the treatment formulation ranges from about 0.01% to 25.0% by weight and more preferably from about 0.1% to 20.0% by weight and most preferably from about 1.0% to 10.0% by weight.

Additional therapeutic agents may be added to the present formulations as medically indicated, selected from the classes of: keratolytics, 10 surfactants, counter-irritants, humectants, antiseptics, lubricants, astringents, wound healing agents, emollients, additional adhesion/coating protectants, additional anti-inflammatory agents, vasoconstrictors, anticholinergics, corticosteroids 15 (e.g. glucocorticoids) and anesthetics. Preservatives and buffers may also be added.

The invention is further illustrated by the following examples:

EXAMPLES

20 Exemplary Hyaluronate Preparations of the Present Invention

The present hyaluronate preparations may be formulated as a solid, gel, paste, cream, salve, lotion, liquid, ointment, and powder, depending on 25 the ingredients and the amounts used.

Example A) Twelve (12) suppositories were prepared containing 0.5% sodium hyaluronate assuming the average weight of the suppository to be 2.0 gm and allowing for a 10% overfill and shrinkage:

- 5 1. Melt 26.268 gm of Polybase_{TM}, a preblended suppository base consisting of a homogenous mixture of various molecular weight polyethylene glycols with a specific gravity of 1.777 at 25°C, in a pyrex beaker over a hot plate or water bath;
- 10 2. add 0.132 gm of finely powdered sodium hyaluronate to the heated Polybase_{TM} with continuous agitation;
3. pour into suppository mold and chill; and
4. trim excess with razor blade or spatula.

15

Calculations: 26.268 gm Polybase_{TM}
+ 0.132 gm Sodium Hyaluronate
= 26.400 gm Total Blend

20

One suppository = 2.0 gm
Each suppository contains 0.5%
(10 mg) sodium hyaluronate.

A total of 12 suppositories were prepared.

25

Example B) Twelve (12) suppositories were prepared containing 1% sodium hyaluronate and 1% hydrocortisone, following the procedure described in Example A:

1. melt 25.872 gm Polybase_{TM};

2. add 0.264 gm Sodium Hyaluronate;
3. add 0.264 gm Hydrocortisone; and
4. repeat steps 3 and 4 of Example A.

5

Calculations: 25.872 gm Polybase_{TM}
+ 0.264 gm Sodium Hyaluronate
+ 0.264 gm Hydrocortisone
= 26.400 gm Total blend

10

One suppository = 2.0 gm

Each suppository contains 1% (20mg)
of sodium hyaluronate and 1%
(20mg) of hydrocortisone.

A total of 12 suppositories were prepared.

15

Example C) A 100 gm sample of a 2 1/2% sodium
hyaluronate cream based formulation was
prepared containing the following components:

20

12.0 gm Sterile H₂O
5.5 gm Propylene glycol
15.0 gm Polyethylene glycol-400
2.5 gm Sodium Hyaluronate
6.0 gm Vehicle-S_{TM}, a preblended aqueous
vehicle containing carboxypolymethylene,
polysorbate 80, simethicone and
methylparaben, 0.18% as a preservative.

25

9.0 gm Polyethylene glycol-8000 (melt)
30.0 gm Polybase_{TM} (melt)
20.0 gm Fattibase_{TM} (melt), a preblended base
consisting of a homogenous mixture of
triglycerides from coconut, palm and palm
kernel oils.

30

100.0 gm Total

Example D) A 2% sodium hyaluronate cream based formulation containing 1% hydrocortisone and 1% pramoxine HCL was prepared containing the following components:

5 14.0 gm Sterile H₂O
 6.0 gm Propylene glycol
 13.0 gm Polyethylene glycol-400
 2.0 gm Sodium Hyaluronate
 1.0 gm Hydrocortisone
10 1.0 gm Pramoxine HCL
 7.0 gm Vehicle-S_m
 9.0 gm polyethylene glycol-8000
 27.0 gm Polybase_m
 27.0 gm Fattibase_m
15 100.0 gm Total

Example E) A 7% hyaluronate cream based formulation containing 5% Lidocaine HCL was prepared containing the following components:

20 15.0 gm Sterile H₂O
 5.0 gm Propylene glycol
 10.0 gm Polyethylene glycol-400
 7.0 gm Sodium Hyaluronate
 5.0 gm Lidocaine HCL
25 6.0 gm Vehicle-S_m
 8.0 gm Polyethylene glycol-8000
 24.0 gm Polybase_m
 20.0 gm Fattibase_m
30 100.0 gm Total

Example F) A 5% hyaluronate ointment containing 2% benzocaine was prepared containing the following components:

5 10 gm Sterile H₂O
5 7 gm Propylene glycol
10 15 gm Polyethylene glycol-400
10 5 gm Sodium Hyaluronate
10 2 gm Benzocaine
10 8 gm Vehicle-S₁
10 10 gm Polyethylene glycol-8000
10 10 gm Polybase₁
15 22 gm Fattibase₁
15 11 gm Aquaphor, a preblended cholesterolized anhydrous water miscible ointment base consisting of petrolatum, mineral oil, mineral wax, and woolwax alcohol.

100 gm Total

20 Example G) Stable gel formulations of hyaluronate were prepared using only water as the vehicle, containing the components as respectively listed:

25 1. 2.5% formulation = 2.5 gm Sodium Hyaluronate
 + 97.5 gm Sterile H₂O (QS)
 Total 100.0 gm of a 2.5% gel formulation.

30 2. 5.0% formulation = 5.0 gm Sodium Hyaluronate
 + 95.0 gm Sterile Water(QS)
 Total 100.0 gm of a 5% gel formulation.

5 Numerous formulations may be derived by varying the concentrations of the above mentioned ingredients of the above Examples and may be determined by the desired characteristics of the finished products. It should also be remembered that other vehicle systems are available for this purpose and therefore this disclosure is not limited to the examples given.

First Exemplary Clinical Evaluation

10 The effaciousness of the present methods of treating anorectal disease states was demonstrated by the following clinical evaluation:

- a. Eighty individuals suffering from external and internal hemorrhoids and rectal fissures were selected for the study.
- 15 b. The patients were randomly divided into two groups: a control group and the test group.
- c. The control group (40 patients) was subjected to standard medical treatment for external thrombosed hemorrhoids. This treatment entailed use of conventional sitz-baths, limited physical activity and conventional controlled diet (e.g. high fiber, low fat). The test group (40 patients) was subjected to the same treatment but also treated with a topical cream containing a specific concentration of sodium hyaluronate as the active ingredient. The three different concentrations of sodium hyaluronate used in this study were: 2.0%, 3.5% and 5.0%.
- 25 d. The hyaluronate preparations were topically applied 2-4 times daily via fingercots by each member of the test group.

5 e. After the initial consultation by the patients with the physician, a nurse contacted each patient by phone every day for one week for the purpose of monitoring each patient. Each patient visited and consulted with the rectal and colon surgeon-physician once a week for a total of five visits. One patient-physician visit/week multiplied by 5 weeks multiplied by 80 patients = 400 patient-physician visits.

10 f. The following parameters were determined and statistically compared: (1) Pain-free time intervals; (2) reduction of swelling (resolving of thrombosed conditions; and (3) general improvement of the anorectum. Hypothesis testing was performed at the 5% significance level.

15 (i) 65.0% of the experimental group (26 patients) experienced pain free time intervals of 4 hours or longer following rectal application of a sodium hyaluronate preparation.

20 (ii) 20% of the control group (8 patients) reported pain free time intervals of one hour or longer following sitz bath treatment.

(iii) No member of the control group reported pain free time intervals greater than 2 hours following standard treatment methods only.

25 (iv) 80% of the control group (32 patients) experienced pain free time intervals of one hour or less following sitz bath treatment only.

5 (v) The experimental group reported less painful bowel movements when a sodium hyaluronate preparation was applied to the anorectal canal within one hour prior to defecation. There were no reported improvements in defecating in the control group following the standard treatment modalities.

10 g. This study conclusively proves the utility and benefit of using the present hyaluronate preparations in the methods of the present invention for treatment of anorectal disease conditions by relieving pain and enhancing healing of injured or diseased anorectal tissues.

15 Second Exemplary Clinical Evaluation

16 The efficaciousness of the present methods of treating anorectal disease states was again demonstrated by the following second clinical evaluation:

20 a. A 2% sodium hyaluronate cream based formulation was prepared containing the following components:

25 2% Sodium hyaluronate
1% Benzyl alcohol
1.5% Sodium propionate
2.25% Fattibase™
0.75% Lecithin
0.75% Glycerin
0.75% Polyethylene glycol - 4000
91% Sterile H₂O

100%

b. Twenty patients suffering from anorectal disorders were selected for the study. The disorders and number of patients having the disorders were as follows:

5

8 patients had either perianal irritation or pruritis ani;

10

4 patients had grade 1-2 bleeding hemorrhoids;

4 patients had fissures (two chronic with sphincter spasm, one superficial and one with a large AIDS (Acquired Immune Deficiency Syndrome) ulceration);

3 patients had prolapsing hemorrhoids; and

1 patient had a thrombosed external hemorrhoid.

15

c. The 20 patients were supplied with 20 gram tubes containing the above 2% sodium hyaluronate preparation. Pile pipe rectal applicators were provided with the tubes for those patients requiring such applicators. The patients were instructed to topically apply the hyaluronate preparation three times each day, either digitally or by applicator as appropriate. The study period was two weeks.

20

d. The patients were initially observed by a physician. The patients were instructed to complete a questionnaire at the end of the two-week study period to determine whether the hyaluronate preparation was effective. The following parameters were determined for each patient:

25

1) the effectiveness of the hyaluronate preparation after application, being rated as effective either a) every time, b) sometime or c) not at all; and

2) the overall effectiveness of the hyaluronate preparation, being rated as a) excellent, b) good, c) fair or d) poor.

5 e. The results of the study showed that 18 of the 20 patients (90%) rated the hyaluronate preparation to be effective either every time (6 patients) or sometime (12 patients). These patients who rated the cream as effective in turn rated the preparation as excellent (6 patients), good (9 patients), and fair (3 patients). Thus, 75% of the patients rated the hyaluronate preparation as good or excellent.

10 (i) The hyaluronate preparation relieved symptoms of itching, burning, bleeding, irritation and pain, depending upon the anorectal disorder.

15 (ii) The two patients who rated the cream as ineffective had anorectal disorders resulting from mechanical type problems.

20 (iii) Significantly, the patient with the AIDS ulceration, which is typically a difficult problem to treat, found great relief by employing the hyaluronate preparation.

25 f. This study conclusively proves the utility and benefit of using the present hyaluronate preparations and the methods of the present invention for treatment of anorectal disease conditions by relieving pain and enhancing healing of injured or diseased anorectal tissues.

While only a few exemplary embodiments of this invention have been described in detail, those skilled

in the art will recognize that there are many possible variations and modifications which may be made in the exemplary embodiments while yet retaining many of the novel and advantageous features of this invention.

5 Accordingly, it is intended that the following claims cover all such modifications and variations.

CLAIMS:

1. A method of treating hemorrhoids and anorectal disease which comprises applying to the hemorrhoids and anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or pharmaceutically acceptable salts thereof.
2. The method of claim 1 wherein said composition includes hyaluronic acid or a pharmaceutically suitable salt thereof in an amount of 0.01 to 25.0% by weight.
3. The method of claim 1 wherein said composition includes hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount of 0.1-20.0% by weight.
4. The method of claim 1 wherein said composition includes hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount of 1.0-10.0% by weight.
- 20 5. The method of claim 1 wherein said composition further includes an additive selected from the group consisting of keratolytics, surfactants, counter-irritants, humectants, antiseptics, lubricants, astringents, emollients, wound healing agents, adhesion/coating protectants, vasoconstrictors, anticholinergics, corticosteroids, anesthetics and anti-inflammatory agents.
- 25 30 6. The method of claim 1 wherein said composition is in a form selected from the group consisting of gel, solid, paste, salve, lotion, liquid, cream, ointment and powder.

7. The method of claim 1 wherein said carrier is water.

8. A method of treating inflammation of anorectal tissues which comprises applying to anorectal 5 tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically suitable salt thereof.

9. A method of treatment for providing a protective coating on hemorrhoids and anorectal diseased 10 tissues which comprises applying an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

10. A method of treatment by promoting 15 healing of hemorrhoids and anorectal disease which comprises applying to hemorrhoids and anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

20 11. A method of treating rectal fissures which comprises applying to rectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

25 12. A method of treating pruritis ani which comprises applying to anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof.

13. A method of treating proctitis which comprises applying to anorectal tissues an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a 5 pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/04594

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07N 1/00; A61K 31/715
US CL :536/55.3, 54, 18.7; 514/54,825

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/55.3, 54, 18.7; 514/54,825

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS (hemorrhoids, anorectal diseases, hyaluronic acid, anti- inflammatory agents, surfactants, corticosteroids, wound healing agents) Dialog (see search terms above)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,736,024 (Della Valle et al) 05 April 1988, ENTIRE DOCUMENT.	1-13
Y	US, A, 3,594,473 (Hunger et al) 20 July 1971, ENTIRE DOCUMENT.	1-13
Y	US, A, 4,808,576 (Schultz et al) 28 February 1989, ENTIRE DOCUMENT.	1-13

Further documents are listed in the continuation of Box C. See patent family annex.

•	Special categories of cited documents:	
•A•	document defining the general state of the art which is not considered to be part of particular relevance	•T• later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
•E•	earlier document published on or after the international filing date	•X• document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
•L•	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	•Y• document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
•O•	document referring to an oral disclosure, use, exhibition or other means	•&• document member of the same patent family
•P•	document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 JULY 1992

Date of mailing of the international search report

20 AUG 1992

Name and mailing address of the ISA/
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 308-4227

Authorized officer

LOUISE LEARY

SD

Telephone No. (703) 308-0196